THE GENERATION AND MAINTENANCE OF IMMUNOLOGICAL MEMORY

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P.T.

National Institute of Allergy and Infectious Diseases
National Institute of Dental Research
National Institute of Arthritis and Musculoskeletal and Skin Diseases

PURPOSE

The National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Dental Research (NIDR), and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH), invite applications for basic immunological research on the generation, maintenance and functional diversity of memory B and T lymphocytes that will define basic mechanisms responsible for the generation, maintenance and functional diversity of memory T and B lymphocytes, in order to provide information needed for improved vaccine development for infectious diseases, and for development of novel therapeutic approaches to the treatment of autoimmune and allergic diseases, as well as transplant rejection. Antigen-specific memory is an essential property of protective immunity, but is poorly understood.
Initial exposure to pathogens activates both non-specific, innate responses and antigen-specific responses of naive T and B cells. However, such initial responses are often insufficient to prevent disease. Immunity that protects the individual against subsequent exposure to the pathogen depends upon the generation of memory T and B cells during initial exposure. Memory lymphocytes must then persist in sufficient numbers, and be readily induced to efficiently eliminate the pathogen upon re-exposure in order to prevent disease.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This PA, The Generation and Maintenance of Immunological Memory, is related to the priority areas of immunization and infectious diseases, HIV infection and maternal and infant health. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No.

017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800).

ELIGIBILITY

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

Traditional research project grant (R01) applications may be submitted in response to this program announcement. Applications for R01 grants may request up to five years of support. Responsibility for the planning, direction, and execution of the proposed research for all applicable mechanisms of support will be solely that of the applicant. Applicants are encouraged to coordinate, through the use of consortium arrangements or subcontracts, integrated approaches with individuals or institutions having relevant reagents and expertise in their use, demonstrated ability in a particular area of relevant research, or access to relevant animal or patient populations.

RESEARCH OBJECTIVES

Background

The success of common vaccines that are given in childhood, such as measles and diphtheria, as well as those used for adults, such as hepatitis B, depends on the ability of the immune system to generate and maintain immunological memory for long periods of time, sometimes throughout life. In addition to their roles in vaccine efficacy, memory lymphocytes also play a role in limiting tumor cell growth, and in mediating allergic responses, autoimmune relapses and the rejection of transplanted organs.

It is known that the initial stimulation of naive T and B cells results in clonal expansion and the production of activated effector cells that secrete antibodies or cytokines, or that mediate target cell killing, and then die. However, some antigen-specific, memory cells persist in a resting state

that differs from that of naive cells, in that memory cells respond more rapidly and more effectively to antigen challenge than do naive cells. The lineage relationships among naive, effector and memory cells, and the events that determine cell death vs memory cell persistence, are not well understood.

Memory in B cells has been studied more widely than memory in T cells, although much remains to be learned. B cell memory induction is known to occur within the germinal centers of secondary lymphoid organs. Memory B cells which have undergone isotype class switching and somatic mutation of immunoglobulin genes can be distinguished by surface phenotype from naive B cells and from terminally differentiated effector B cells (plasma cells). Recent studies have begun to identify the molecules, such as CD40, that play important roles in determining B cell fate. Antigen persistence, in the form of immune complexes concentrated on follicular dendritic cells within germinal centers, is thought to be important for the persistence of B cell memory.

The study of T cell memory has been confounded by the difficulty in distinguishing among naive, effector and memory T cells. Currently, there are no convenient markers that identify memory T cells unambiguously. Although functional long-term T cell memory has been repeatedly demonstrated for both CD4 and CD8 T cells, a number of important questions regarding T cell memory remain to be answered. One controversial, but very important, issue is whether T cell memory, like B cell memory, depends on antigen persistence. If continued or intermittent restimulation is needed to protect memory T cells from death, residual antigen, crossreactive antigen, or non-specific interactions might be involved. There also may be different subsets of memory T cells with different requirements for re-activation or for maintenance. The molecular basis for death vs memory cell development following naive T cell activation is not well defined. In addition, the potential to modify the cytokine profiles of memory T cells re-activated in vivo is poorly understood, and this area is especially relevant to the development of immunomodulatory regimes for intervention in allergy, autoimmunity and transplantation.

Research Objectives and Scope

The fundamental importance of research on immunological memory for application to the treatment of human disease provides a strong impetus for expanded efforts to identify those factors that regulate the generation, maintenance and functional diversity of memory B and T cells. Innovative approaches are sought to identify the genetic, biochemical, cellular and systemic components of immune memory that might serve as targets for therapeutic intervention. Investigators are encouraged to propose creative experimental approaches for well-defined

studies in human or animal systems. Examples of potential research topics include, but are not limited to:

o phenotypic markers that identify memory vs naive and effector lymphocytes, and lineage relationships among naive, effector and memory lymphocytes;

o molecular events that determine whether lymphocyte activation results in memory vs cell death;

o mechanisms that regulate the longevity of immune memory, such as antigen persistence, tissue localization or cytokine environment;

o differences in memory within lymphocyte subsets, such as Type-1 vs Type-2 T cells, gamma/delta TCR vs alpha/beta TCR T cells;

o differential requirements for activation or tolerance induction in memory vs naive lymphocytes;

o differential functional responses of memory vs naive cells, and the potential for intervention to alter memory responses qualitatively;

o differences in memory induction via mucosal vs systemic routes of immunization; and

o the basis for different memory responses in neonatal, adult and aged populations.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects unless a clear and compelling rationale and justification are provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research", which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and the NIH Guide for Grants and Contracts, Vol. 23 No. 11, March 18, 1994.

Investigators may obtain copies from these sources or from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev.5/95) and will be accepted on the standard application deadlines as indicated on the application kit. Application kits are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone (301) 435-0714, email: asknih@od.nih.gov.

For purposes of identification and processing, item 2 on the face page of the application must be marked "YES". The PA number and the PA title, "THE GENERATION AND MAINTENANCE OF IMMUNOLOGICAL MEMORY," must also be typed in section 2.

The completed, signed original and five legible, single-sided copies of the application must be sent or delivered to:

CENTER FOR SCIENTIFIC REVIEW (formerly Division of Research Grants)
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817-7710 (for express/courier service)

Applicants from institutions that have a General Clinical Research Centers (GCRC) funded by the NIH National Center for Research Resources may wish to identify the Center as a resource for conducting the proposed research. If so, a letter of agreement from the GCRC Program Director must be included in the application material.

REVIEW CONSIDERATIONS

Review Procedures

Applications will be assigned on the basis of established PHS referral guidelines. Upon receipt, applications will be reviewed for completeness by the NIH Center for Scientific Review (CSR).

Incomplete applications will be returned to the applicant without further consideration. Applications will be reviewed for scientific and technical merit in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council.

Review Criteria

The five criteria to be used in the evaluation of grant applications are listed below. To put those criteria in context, the following information is contained in instructions to the peer reviewers.

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. The reviewers will comment on the following aspects of the application in their written critiques in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered by the reviewers in assigning the overall score weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have a major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

2. Approach. Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation. Does the project employ novel concepts, approaches or method?
Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

4. Investigator. Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

5. Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

The initial review group will also examine: the appropriateness of proposed project budget and duration; the adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research and plans for the recruitment and retention of subjects; the provisions for the protection of human and animal subjects; and the safety of the research environment.

AWARD CRITERIA

Applications will compete for available funds with all other favorably recommended applications. The following will be considered when making funding decisions: quality of the proposed project as determined by peer review, program balance, and availability of funds.

INQUIRIES

Written and telephone inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Inquiries regarding programmatic (research scope, eligibility and responsiveness) issues may be directed to:

Helen Quill, Ph.D.
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
6003 Executive Boulevard, Room 4A22
Bethesda, MD 20892-7640
Telephone: (301) 496-7551
FAX: (301) 402-2571
Email: hq1t@nih.gov

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Division of Extramural Research
National Institute of Dental Research
Building 45, Room 4AN-32F
Bethesda, MD 20892-6402
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FAX: (301) 480-8318
Email: Dennis.Mangan@nih.gov

Dr. Susana Serrate-Sztein
Rheumatic Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building, Room 5AS37G
Bethesda, MD 20892
Telephone: (301) 594-5032
FAX: (301) 480-4543
Email: szteins@exchange.nih.gov

Direct inquiries regarding fiscal matters to:

Celeste Kerner
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
6003 Executive Boulevard, Room 4B26
Bethesda, MD 20892-7610
Telephone: (301) 402-6213
FAX: (301) 480-3780
Email: ckerner@mercury.niaid.nih.gov

Mr. Martin Rubinstein
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Email: Martin.Rubinstein@nih.gov

Ms. Carol Fitzpatrick
Grants Management Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building, Room 5AS43K
Telephone: (301) 594-3506
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Email: fitzpatric@ep.niams.nih.gov

Although the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is not a co-sponsor of this PA, NIDDK does have an interest in this area, and can be contacted through:

Dr. David Badman
Hematology Program
National Institute of Diabetes and Digestive and Kidney Diseases
Natcher Building, Room 6AS13C
Bethesda, MD 20892
Telephone: (301) 594-7717
FAX: (301) 480-3510
Email: David_Badman@nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos.93.855, 93.121, and 93.366. Awards are made under authorization of the Public Health Service Act, Sec. 301(c), Public Law 78-410, as amended. Awards will be administered under PHS grants policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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